# Guidance for Industry

## Major, Minor, FAX, and Telephone Amendments to Original Abbreviated New Drug Applications

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**May 2000**
**Revision 1**

**OGD**

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## I. INTRODUCTION

This guidance is intended to document the Office of Generic Drugs (OGD) policy regarding the determination of major, minor, FAX, and telephone amendments to original abbreviated new drug applications (ANDAs).[2] This guidance is a revision of the August 1999 guidance. It explains that the issuance of a major, minor, *or FAX* amendment will stop the review clock.

## II. POLICY

### A. How does the Office Of Generic Drugs classify amendments?

Generally, the considerations used to categorize amendments requested by OGD are determined by the nature of the chemistry, manufacturing, and controls (CMC), microbiology, labeling, and/or bioequivalence deficiencies.

OGD classifies requested amendments to abbreviated new drug applications (ANDAs) as major, minor, FAX, or telephone. Major amendments have the same review priority as original, unreviewed ANDAs and are reviewed consistent with OGD's first in-first reviewed procedure. Minor amendments have a higher review priority than major amendments because they often

[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency=s current thinking on the classification of amendments to original ANDAs. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] This includes revision and clarification of the policy stated in Policy and Procedure Guide (PPG) 38-93, ARestatement of the Office of Generic Drugs= >First-In, First-Reviewed= Policy and Modification of the Exceptions to the Policy Regarding Minor Amendments,@ relating to original ANDAs.

mean an application is close to approval and should, therefore, be given priority. The issuance of major, minor, and FAX amendments stops the review clock while the applicant addresses the deficiencies noted by OGD, but telephone amendments do not stop the clock unless the applicant does not respond within the anticipated time. Telephone amendments represent the reviewer's highest priority work assignments with FAX amendments considered the next highest priority.

**B. When is an amendment classified as major?**

In general, OGD classifies an amendment as *major* if ***any*** of the following criteria apply at the time of the determination:

1. An experienced chemistry reviewer cannot reasonably be expected to review the requested information in less than one hour (excluding time needed to retrieve the application and to prepare the review documentation and action letter).

2. An experienced microbiology reviewer cannot reasonably be expected to review the requested microbiological/sterility assurance data in less than one working day (excluding time needed to retrieve the application and to prepare the review documentation and action letter).

3. The amendment will provide data to address major bioequivalence (BE) deficiencies (e.g., there is a need to conduct one or more bioequivalence studies and resubmit data).

4. Information in addition to that requested by OGD is being submitted in response to a request for a minor, FAX, or telephone amendment (e.g., additional and/or new strengths or manufacturing facilities for the drug substance or drug product), and the review will require more than one hour to complete.

Examples that may be determined to be major amendments include, but are not limited to:

- The submission is of such overall poor quality that only a general review can be conducted and only broad, rather than product-specific deficiencies can be identified.

- No letter of authorization (LOA) is provided to permit the review of the applicable drug master file (DMF) for the drug substance, or a drug release-controlling component of a therapeutic system.

- The ANDA contains little or no validation data for appropriate analytical methods (e.g., chromatography).

- The stability data submitted are inadequate to justify the proposed expiration dating and the stability studies must be repeated.

- The test batch is determined not to be representative of the proposed production batch, necessitating the manufacture of a new test batch.

- The applicant submits a procedure for reworking a batch in the absence of adequate data to justify the proposed procedure.

- The bioequivalence study is unacceptable (e.g., a new or additional study is needed, such as an in vitro BE study for nasal sprays), even if chemistry deficiencies may be designated as minor or FAX in nature.

**C. When is an amendment classified as minor?**

OGD categorizes an amendment as *minor* when none of the above major criteria apply, and ***all*** of the following criteria that are relevant apply at the time of the determination:

1. An experienced chemistry reviewer can reasonably be expected to review the CMC data in less than one hour (excluding time required to retrieve the application and to prepare the review documentation and response).

2. An experienced microbiology reviewer can reasonably be expected to review the requested microbiological/sterility assurance information in less than one working day (excluding time needed to retrieve the application and to prepare the review documentation and action letter).

3. It is expected that the applicant will need more than 30 days to respond with a complete amendment.

4. No significant bioequivalence deficiencies (e.g., a need to conduct a new bioequivalence study or in vitro BE testing for nasal sprays) have been identified at the time the minor amendment determination is made. Less significant bioequivalence deficiencies (e.g., dissolution data) may have been identified.

5. The remaining factors precluding approval are generally considered to be outside the immediate control of the applicant (e.g., DMF deficiencies).

Examples that would result in a minor amendment determination include, but are not limited to:

- Data are requested to support compendial testing requirements, including endotoxin or preservative effectiveness testing.

- There are presently unresolved current good manufacturing practices (CGMP) issues that have been identified by the Office of Compliance affecting one or more of the facilities listed in the application (e.g., withhold recommendations), even if all other review aspects of the ANDA are considered sufficient.

- There are labeling deficiencies that have not been adequately addressed in a timely manner for an application that is otherwise sufficient for approval, excluding an acceptable establishment evaluation request from the Office of Compliance.

**D. When is an amendment classified as a FAX amendment?**[3]

OGD classifies an amendment as a *FAX* amendment when the above minor criteria, except section II.C.3, apply and ***all*** of the following criteria that are relevant apply at the time of the determination:

1. All deficiencies are judged to be within the immediate control of the applicant.

2. All relevant DMFs have been found acceptable.

3. OGD expects that the applicant will be able to provide a complete response to all deficiencies within 30 calendar days from the request date.

Examples of FAX amendment determinations include, but are not limited to:

- Deficiencies that are primarily administrative or clerical revisions, such as:

  - Inconsistent statements in the ANDA need to be clarified, but it is unlikely that the clarifications will result in further questions.

[3] OGD will accept only hard copies (2) of major and minor amendments for review. However, OGD will review responses to FAX and telephone amendments transmitted by facsimile provided the applicant also submits hard copies (2).

- OGD has requested a specific change that will not result in additional data submission (e.g., to add a particular test, to monitor the temperature in stability studies, to add limits for acceptance or other specifications based on already submitted test results, or to make minor manufacturing revisions).

- The amendment involves resubmission of illegible pages or correction of typographical errors.

- Commitments are needed to provide certain items postapproval (e.g., postapproval statements on the source of the active ingredient on stability data reports, or provision of a batch record and dissolution data for the first postapproval production batch).

- Commitment is needed to submit a supplemental application for approval.

- The applicant is asked to provide additional stability data accrued during the review process.

### E. When is an amendment classified as a telephone amendment?[4]

An amendment is classified as a *telephone* amendment if it follows a *minor* or FAX amendment and the new amendment meets the following criteria:

1. It primarily addresses an administrative or minor technical issue, and

2. OGD believes the applicant can provide a complete and satisfactory response within 10 calendar days of the call, and

3. The deficiencies are similar to those described for a FAX amendment.

Examples of telephone amendments include, but are not limited to:

- Clarification of data already submitted

- Request for a postapproval commitment

[4] OGD will accept only hard copies (2) of major and minor amendments for review. However, OGD will review responses to FAX and telephone amendments transmitted by facsimile provided the applicant also submits hard copies (2).

To expedite the review, telephone amendments may also be requested during the final office level administrative review of an ANDA, immediately prior to tentative or final approval.

## III. REVIEW CONSIDERATIONS

### A. What are the time frames for handling amendments?

OGD attempts to review major amendments within 180 days and to review minor amendment within 60 days. However, not all minor amendments can be reviewed within 60 days (e.g., if consults from outside of OGD are needed).

### B. When is an amendment redesignated?

Deficiencies that are not satisfactorily addressed by the applicant after the review of the FAX amendment will be communicated back to the applicant as a minor amendment or a telephone amendment, based on the criteria in section II.

There could be situations in the review of an ANDA that result in the redesignation of an amendment and consequently the status of the ANDA. For example, the chemistry review and the microbiology review of an ANDA may be completed in different timeframes. If the chemistry review is completed first and the appropriate criteria are met, OGD will issue a request for a minor amendment response to the deficiencies. If the microbiology review subsequently reveals major deficiencies, these will be communicated to the applicant as a request for a major amendment response. This action will also change the chemistry response to a major amendment.

In some cases the results of a bioequivalence or labeling review will result in the redesignation of an amendment. For example, if an ANDA is in minor status for chemistry and it is subsequently determined that an in vivo bioequivalence study fails, a redesignation to major will occur.

Examples that could result in amendment redesignation include:

- A FAX amendment request that has not been responded to within 30 days will be converted into a minor amendment request.

- A chemistry or microbiology telephone amendment request that has not been responded to within 10 days of OGD's request will be redesignated as a minor amendment.

In general, OGD will not consider a request to reclassify an amendment because certain deficiencies are eliminated by an applicant's withdrawal of a portion of the application.

### C. What is the process for classifying an amendment?

Reviewers will conduct their review according to OGD policies. The reviewer makes the initial recommendation to the team leader regarding classification of the amendment to be requested. The team leader will conduct the secondary review and concur with the amendment classification, if appropriate. Division directors (or deputies) will complete any necessary tertiary reviews. If an applicant requests reclassification of an amendment, the director or deputy will review that request. Applicants are expected to respond to all requests for amendments in a timely manner and ensure that two hard copies are submitted of any material communicated to OGD by facsimile or telephone.

Labeling reviewers will transmit labeling deficiencies directly to the applicant via facsimile in the absence of any CMC, microbiology, or bioequivalence deficiencies, or in the event the labeling review is completed after the remaining deficiencies have been communicated to the applicant. Unless otherwise specified, labeling deficiencies will be issued by facsimile.